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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/929,771	08/14/2001	Robert T. Lum	96,877-V1	2294

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EXAMINER
BERCH, MARK L

ART UNIT	PAPER NUMBER
1624	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/929,771	Applicant(s) LUM ET AL.
	Examiner Mark L. Berch	Art Unit 1624

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *48-50,53-62,65-68,70-73 and 76-79* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *48-50,53-62,65-68,70-73 and 76-79* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/7/03 has been entered.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 48-50, 53, 56-57, 61, 68, 70-73, 76, 77-79 are rejected under 35 U.S.C. 102(a) as being anticipated by WO 97/16452.

Note formula I and species therein which deal with 6- (substituted anilino) species. The utility is the same. The claims in this case are not supported by the disclosure of the 08/692012 parent.

It appears that an impasse has been reached on this point. Applicants insist that their claims are entitled to the 8/2/1996 date of 08/692012. These claims are not even

entitled to the instant filing date, because they lack description in this specification, for reasons given below in the two description rejections.

Applicants' reasoning that the material actually in WO 97/16452 is "within the scope of the ... parent application" is legally unsound. The priority date for claims is determined without reference to the contents of the prior art reference. Once the claims have been determined to lack benefit, they are properly rejected. Attention is drawn to *In re Schreiber*, 199 USPQ 82, which had this exact situation.

Applicants also argue that "there is very little overlap between WO 97/16452 and the present application." Applicants cite the definition of R4 and R5. This is entirely mistaken. The definition for these two variables in the current claims is H or alkyl, which alkyl can be optionally substituted with one of 5 substituents. That definition embraces many of the compounds. At any rate, it only takes one species to anticipate. Examples 1, 2, 4, 6, 8, 9, etc all anticipate. The fact that there are examples in the reference which do not anticipate is of no legal significance.

Claims 48-50, 53, 56-57, 61, 68, 70-73, 77-78 are rejected under 35 U.S.C. 102(b) as being anticipated by Norman.

The species named in the second paragraph of page 7431, column 2 is not subject to the proviso as it is a substituted benzyl. This species is NOT olomoucine. The utility is the same. As for the date issue, this was discussed above. The fact that this species in the priority document is of no significance to these generic claims, as they themselves

The rejections over McAfee, Seyama are eliminated by the fact that R3 can only be an amino group.

The rejections made in the parent over Kaneko and WO 93/17020 are not included because R_2 = substituted heterocyclic and hydroxy-cyclopentyl respectively is no longer permitted. The rejection made in the parent over Breshears is not included because R_2 = H is no longer permitted. The rejections made in the parent over Bader and Liotta are not included because R_1' = halogen is no longer permitted.

Claims 48-50, 53, 56-57, 61, 68-73, 76 are rejected under 35 U.S.C. 102(b) as being anticipated by De Azevedo.

The reference is from the January 1997 issue. It discloses roscovitine, shown in page 520. The same biochemical property is disclosed. Note that the first proviso no longer covers this species, since it has 9-isopropyl. The date issue is as discussed above.

Claims 48-50, 53, 56-57, 61, 68-73, 76 are rejected under 35 U.S.C. 102(b) as being anticipated by 6316456.

This is the US equivalent of the WO 97/20842 reference cited previously. With the reshaped claims, this reference is no longer merely renders the claims obvious, but now anticipates. Table 1, species 1-6, 10, 14-16 all anticipate.

Claims 48-50 are rejected under 35 U.S.C. 102(b) as being anticipated by Jacobsen.

See the iodobenzyl species 15, 17-20, which avoid all provisos.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 48-50, 56-57, 61, 68, 70-73, 77-78 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vesely.

The reference discloses olomoucine, which the proviso removes from claim 1. However, the 6-(α,α-dimethylbenzylamino) derivative would be the same as the prior art, just with two extra methyls on the α carbon of the benzyl. Compounds that differ only by the presence or absence of an extra methyl group or two are homologues. Homologues are of such close structural similarity that the disclosure of a compound renders *prima facie* obvious its homologue. The homologue is expected to be preparable by the same method and to have generally the same properties. This expectation is then deemed the motivation for preparing homologues. Of course, these presumptions are rebuttable by the showing of unexpected effects, but initially, the homologues are obvious even in the absence of a specific teaching to add or remove methyl groups. See *In re Wood,* 199 USPQ 137; *In re Hoke,* 195 USPQ 148; *In re Lohr,* 137 USPQ 548; *In re Magerlein,* 202 USPQ 473; *In re Wiechert,* 152 USPQ 249; *Ex parte Henkel,* 130 USPQ 474; *Ex Parte Fischer* 96 USPQ 345; *In re Fauque,* 121 USPQ 425; *In re Druey,* 138 USPQ 39. In all of these cases, the close structural similarity between two compounds differing by one or two methyl groups was itself sufficient show obviousness. See also MPEP 2144.09, second paragraph. The utility is the same.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 48-50, 53-57, 59-62, 65-68, 70-73, 76-78 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. A number of the claim 71 disorders are not considered a "cell proliferative disorder". a) Gout is a manifestation of hyperuricemia. Crystals of sodium urate cause acute inflammatory arthritis. It is not treated with antiproliferative agents. Symptoms are treated with anti-inflammatory agents. Gout itself is treated with Colchicine , a microtubule inhibitor which appears to inhibit migration of white cells to affected joints and Allopurinol which is a competitive inhibitor of xanthine oxidase and thus causes excretion of hypoxanthine and xanthine instead of conversion to urate. b) Multiple Sclerosis is of unknown cause, although it may be of immunological origin. It is not characterized by cell proliferation, but is a destruction of the preformed myelin. Treatment does not involve standard antiproliferative agents, but instead involves the use of corticosteroids, and even that is for symptom relief; it does not treat the underlying disorder. c) Similarly, lupus (SLE is assumed) arises from hyperactivity of the immune system. d) Type I diabetes is a disorder of the carbohydrate mechanism caused by little or no endogenous insulin. It is correct that lymphocytes destroy the

beta-cells in the islets of Langerhans, whereas the lymphocytes should not do that. This does not mean that Type I diabetes is a "cell proliferative disorder". e) Rheumatoid arthritis is generally classified as an autoimmune disorder, but applicants seem to be assuming that any autoimmune disease by its very nature is a "cell proliferative disorder", which is simply not true. f) "host vs graft disease" is not a proliferative disorder. It is in fact the normal, albeit undesired, reaction of the host T-cells to the foreign graft. The earlier traverse here appears to completely misunderstand the meaning of "cell proliferative disorder." A cell proliferative disorder is anything that causes any abnormal cell growth. That can be growth by cellular proliferation more rapidly than normal, or continued growth after the stimulus that initiated the new growth has ceased, or lack (partial or complete) of structural organization and/or coordination with surrounding tissue. The remarks seem to indicate that applicants are using a vastly broader definition, in which "cell proliferative disorder" is any disorder in which the proliferation (growth) of cells is part of the body's response. It is correct that there is cell growth e.g. monocytes in the case of gout in the body's response to the urate crystals. But that does not make it a "cell proliferative disorder" according to the normal understanding of the term. If applicants definition of the terms were to be used, nearly all diseases will qualify as a "cell proliferative disorder" , since nearly all involve some sort of cell growth.

2. The second proviso does not make sense, since it refers to values of R3 which are not permitted in the first place.
3. In the first two provisos, the terms should be R_1', not R_1.

4. The third proviso refers to R3 as not being alkyl, but R3 cannot be alkyl any more, so this proviso is pointless.
5. The fifth proviso should be R_1'X, not R_1X.

Claim 68, 70-72 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

There is no practical way to determine what the scope of claim 68 is. Specifically, who is "in need thereof"? It is entirely possible that the claim covers all known diseases, and thus anyone with any disease is in need thereof. Perhaps it covers even healthy people? There is no evidence that one of ordinary skill in the art knows who is in need of this inhibition and who is not, because so little is known about the actual, practical, effects of administering CDK2 inhibitors. Determining whether a given disease responds or does not respond to such inhibition will surely involve undue experimentation. Suppose that a given CDK2 Inhibitor X when administered to a patient with Disease D does not obtain a response. Does one then conclude that Disease D does not fall within this claim? Keep in mind that:

A. It may be that the next patient will respond. It is quite common for pharmaceuticals to work only with some people, not all. Thus, how many need to be tested?

B. It may be that the wrong dosage or dosage regimen was employed. It is quite common for pharmaceuticals to work at one dosage, but not at another which is significantly higher or lower. Furthermore, the dosage regimen may be vital --- should the drug be given e.g. once a day, or four times in divided dosages? Thus, how many

dosages and dosage regimens must be tried before one is certain that this pharmaceutical won't affect Disease D?

C. It may be that X simply isn't potent enough for Disease D, but that another inhibitor Y is potent enough, so that D really does fall within the claim. Thus, how many different inhibitors must be tried before one concludes that D doesn't fall within the claim?

D. Conversely, if D responds to Y but not to X, can one really conclude that D falls within the claim? It may be that the X result is giving the accurate answer, and that the success of Y arises from some other unknown property which Y is capable of. Thus, when mixed results are obtained, how many more pharmaceuticals need be tested?

E. Finally, suppose that X really will work, but only when combined with Z. There are for example, agents in the anticancer technology which are not themselves effective, but the disease will respond when the agents are combined with something else.

The same is true for the dependent claims as well. There is no way of knowing which cancers are covered by claim 72 and which are not. There is no standard list of cancers that one can consult to determine that a given cancer does not fall within claim 72.

As a result, determining the true scope of the claim will involve extensive and potentially open-ended research. Without it, one skilled in the art cannot determine the actual scope of the claim. Hence, the claim is indefinite. The earlier traverse does not comes to terms with the rejection. It says that it covers "only those diseases attributable

to the undesired proliferation of cells." No such limitation actually appears in claim 68, which makes no mention of proliferation.

The recent traverse is unpersuasive as well. In this regard, the remarks give a quotation of the text of claim 68 which is not accurate. As for the two patents cited, a) different specifications will support different claim language, and b) the claim 68 language does not actually appear in either patent.

Claims 48-50, 53-57, 59-62, 65-68, 70-73, 76-78 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The provisos lacks description. Even a negative limitation requires description, *Ex Parte Grasselli,* 231 USPQ 393. Specifically:

The first proviso does not resemble any of the 4 provisos given on page 6, lines 8-14 of the specification. For example, it mentions the phenethyl-amino choice for R1', and the R2 choice of ethyl, neither of which are referred to in those four provisos. The 4th proviso deals with an alkyl substituted by a heteroaryl, which is not mentioned in those four provisos.

The examiner is not stating that applicants cannot amend their claims, only that negative limitations require description.

Claims 48-50, 53-57, 59-62, 65-68, 70-73, 76-78 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that

the inventor(s), at the time the application was filed, had possession of the claimed invention.

In both of these claims, R2 and R3 are fixed, so that claim 58 is a subgenus of 4 species, and claim 79 is a subgenus of 7 species. Where is such a subgenus set forth? A claim to a subgenus requires that the specification convey that applicants did indeed possess that particular subgenus. Cf *In re Smith,* 173 USPQ 679, *In re Cother,* 168 USPQ 773, 777; *Tosan v. Siegel,* 167 USPQ 361; *In re Kaufmann,* 172 USPQ 124; *Ex parte Haas,* 188 USPQ 374; *Ex parte Winters,* 11 USPQ2d 1387; *Yamada v. Aggarwal,* 57 USPQ2d 2002. Note particularly *Fujikawa v. Wattanasin,* 39 USPQ2d 1895, 1904: " ... his application contained no blazemarks as to what compounds, other than those disclosed as preferred, might be of special interest. In the absence of such blazemarks, simply describing a large genus of compounds is not sufficient to satisfy the written description requirement as to particular species or subgenuses. ... just because a moiety is listed as one possible choice for one position does not mean there is ipsis verbis support for every ... sub genus that chooses that moiety." The *Ex parte Winters,* 11 USPQ2d 1387 decision is particularly relevant, since it deals with a subgenus of 4 compounds, exactly the case with claim 58 here.

Claim 68 and 70-73 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The treatment of "proliferative disorders", including cancer, in general, is not enabled.

Pursuant to *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), one considers the following factors to determine whether undue experimentation is required: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. Some experimentation is not fatal; the issue is whether the amount of experimentation is "undue"; see *In re Vaeck*, 20 USPQ2d 1438, 1444.

The analysis is as follows:

(1) Breadth of claims.

(a) Scope of the compounds. Owing to the open-ended nature of "substituted alkyl" and "substituted aryl", the genus coves millions of compounds.

(b) Scope of the diseases covered. The coverage is unclear, but could be immense. As noted above, it is not clear which proliferative disorders are not embraced, but it is entirely possible that all proliferative disorders are embraced, if CDK2 plays a role in all of them. There are hundreds of types of cancers and tumors. They can occur in pretty much every part of the body. Further, "proliferative disorder" is much broader. A proliferative disorder is anything that causes any abnormal tissue growth. That can be growth by cellular proliferation more rapidly than normal, or continued growth after the stimulus that initiated the new growth has ceased, or lack (partial or complete) of structural organization and/or coordination with surrounding tissue. It can be benign or malignant. Thus, such a term might cover not only all cancers, but also covers

precancerous conditions such as lumps, lesions, and polyps. In addition, it may well embrace various non-cancerous proliferative disorders such as certain types of restenosis, vascular smooth muscle proliferation associated with atherosclerosis, glomerular nephritis, clonal proliferative disorders including the various Myelodysplastic Syndromes such as Refractory anemias, certain types of abnormal wound healings, different types of abnormal angiogenisis, pulmonary fibrosis, macular degeneration, myeloproliferative disorders such as primary polycythemia and myleofibrosis, an assortment of skin disorders (such as psoriasis, palmoplantar Pustulosis, keratinisation disorders, keratosis, lichenified eczema, and seborrhoeic dermatitis), LAM (Lymphangioleiomyomatosis, a smooth muscle proliferative disorder of the lungs) and rheumatoid arthritis. There is no such thing that an agent which is effective against such disorders generally, since they are so diverse, nor is there any reason to think that such an agent could be made to work.

(2) The nature of the invention and predictability in the art: The invention is directed toward medicine and is therefore physiological in nature. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

(3) Direction or Guidance: That provided is very limited. The dosage range information given on page 16 is a 10,000 fold range and hence is largely useless. Further, it is completely generic as to the disease being treated. In terms of specific cancers, none are named.

(4) State of the Prior Art: The prior art knows that there never has been a compound capable of treating cancer generally. There are compounds that treat a modest range of cancers, but no one has ever been able to figure out how to get a compound to be effective against cancer generally, or even a majority of cancers. Thus, the existence of such a "silver bullet" is contrary to our present understanding in oncology. Even the most broadly effective antitumor agents are only effective against a small fraction of the vast number of different cancers known. This is true in part because cancers arise from a wide variety of sources, such as viruses (e.g. EBV, HHV-8, and HTLV-1), exposure to chemicals such as tobacco tars, genetic disorders, ionizing radiation, and a wide variety of failures of the body's cell growth regulatory mechanisms. Different types of cancers affect different organs and have different methods of growth and harm to the body, and different vulnerabilities. Even those that affect just a single organ are often not generally treatable. As an example, the main types of lung cancer are small cell (oat cell), giant cell, clear cell, adenocarcinoma of the lung, squamous cell cancer of the lung, and mesothelioma. There is no such thing as a treatment of these generally because of their diversity. That is, there is no one compound that can treat these generally, or even most of them, nor is there any reason to think that there could be such a compound.

The Sielecki reference is cited to show the specific state of the art in this field. It is dated 2000, and hence is actually several years later than the alleged filing date of 1996 or 1997. As can be seen from this, as of 2000, not a single CDK2 inhibitor had actually been made into a working pharmaceutical, or even tested as an anticancer agent. The reason for this was explicitly stated in the conclusion on page 12: "However,

our understanding of the biology and structural features required to selectively mediate cell progression is still in its infancy." That is clear evidence that more than routine experimentation will be needed. The essay goes on to set forth fundamental understandings that are still lacking, noting that "With increased understanding, maybe we can drive discovery toward yet more selective and effective therapies." This is again evidence that the level of skill in this art is low.

Another important fact can be seen in the page 13 table. Note in the "key CDK Inhibitors", olomoucine, the lead compound in this area. Applicants compounds are close olomoucine analogues (the genus embraces olomoucine, which is removed by proviso). Note that olomoucine is the weakest compound in the table, and indeed, so far as the examiner is aware, olomoucine never even progressed to animal trials as an anti-cancer agent. However, the testing presented in Table 6 of the specification established that many of these compounds are either less effective as CDK2 inhibitors than olomoucine (the first compound in the Table), or are not effective to actually inhibit cell proliferation even in this crude test, or both. Indeed, a number of species displayed no measurable activity in either test. Thus, in the first 9 actually tested in the second column test (not counting the first, the olomoucine) on page 47-48, five of them have IC(50) values (see last column) which are so high that they have virtually no meaningful potency, and four had no demonstrated activity at all. The specification says that cell proliferation inhibition has an IC(50) of "preferably less than 0.5 μg/ml" which is a reasonable standard, but only 4 species in the entire table met that standard; the other 20 species, many in the 48-77 range, tested did not. Even on this very simple *in vitro* test, the results show that most compounds are essentially ineffective. Even in terms of

inhibiting the enzyme, the second from rightmost column, many of the compounds showed no activity. Applicants argue that the examiner has not supported his doubts, but those are the very facts which justify the doubts. Applicants are claiming vastly more than has ever been made to work for olomoucine, using compounds which are for the most part weaker than olomoucine.

(5) Working Examples: There are no working examples to the treatment of any disease at all. The sole cancer screen done appears on page 50. At 3 dosage regimens, the tested species met the minimum standard of efficacy, T/C = 130. However, compound 3 is by far the most potent as in Table 6. In terms of the ability to inhibit cell proliferation, the next most potent compound tested had only 1/6 its potency and hence would not be expected to pass even this crude screening test with L1210. The evidence of record is thus that this compound is not representative of the genus as a whole; it is by far the most potent, in terms of CDK2. No one would possibly argue that such a test shows efficacy against cancer generally.

In addition, there are cited four earlier references. Glab(1994) does not mention therapeutic utility. Others present use only as a possibility to be achieved by developing much better compounds. For example, Vesely (1994) says, "It is possible that, through its specificity, olomoucine may lead to a compound which will preferentially inhibit the proliferation of certain tumor cells." Olomoucine is excluded by proviso from the claims. This shows that basic research is still required to obtain the necessary selectivity. Abraham (1995) says that "olomoucine may constitute a lead compound for the design of new anti-tumor agents." Similarly, Schultz-Gahmen (1995) referring to its results, says it "should prove useful in modifying and improving the lead compound." But, a lead

compound is one which is not actually ready for use; it is by its nature something which needs to be modified by additional research.

(6) Skill of those in the art: It is beyond the skill of oncologists today to get an agent to be effective against cancers generally, evidence that the level of skill in this art is low relative to the difficulty of such a task. The skill thus depends on the particular cancer involved. There are cancers where the skill level is high and there are multiple successful chemotherapeutic treatments. In many, many cancers, however, there is no chemotherapy whatsoever available. As an example, one skilled in the art knows that chemotherapy of brain tumors is especially difficult. This is because 1) the blood-brain barrier, which is often intact in parts or all of a brain tumor, will block out many drugs, as it is the purpose of the blood-brain barrier to protect the brain from alien chemicals, and 2) CNS tumors are characterized by marked heterogeneity, which greatly decreases vulnerability to chemotherapy. As a result, many categories of CNS tumors simply have no chemotherapy available. These include, generally, hemangiomas and hemangioblastomas, low grade gliomas, meningiomas, craniopharyngiomas, acoustic neuromas, pituitary adenomas, optic nerve gliomas, glomus jugulare tumors and chordomas, to name just some. The majority of common cancers do not respond to chemotherapy. With regard to non-cancerous proliferative disorders, the skill level is quite varied, disease by disease. Thus, for e.g. psoriasis, the skill level is moderate, for LAM, it is quite low. As for the skill level in this very specific area, see the discussion of Sielecki as noted above.

(7) The quantity of experimentation needed: Given the fact that historically the development of new cancers drugs has been difficult and time consuming, and

especially in view of factors 1, 3, 6 and 4, the quantity of experimentation needed is expected to be great.

With regard to the dependent claims, it should be noted as indicated above, that 6 of the 8 disorders listed in claim 71 are not in fact proliferative disorders at all. The inclusion of gout in claim 71 makes no sense at all. These compounds are purines. Patients with gout are normally told to avoid high purine foods, in order to reduce uric acid secretion. The traverse is unpersuasive, and does not deal with the issue raised. Instead, the earlier argument appears to have been that these compounds will "reduce the number of proliferating clones of immunocytes", but there is no evidence whatsoever that this is true. Systemic lupus erythematosus (SLE) is a complex disorder, an autoimmune disease characterized by immune dysregulation resulting in the production of antinuclear antibodies (ANA), generation of circulating immune complexes, and activation of the complement system. It is a difficult disorder which can be fatal. Applicants had pointed out that treatments include anti-neoplastic agents. This is true, methotrexate is used. But so far as the examiner is aware, methotrexate is not a CDK-2 inhibitor. It is true that cell growth is involved in Lupus. However, cell growth is involved in the vast majority of diseases, so by this reasoning, applicants compounds would be effective for most diseases, period. Applicants have presented no nexus between SLE and CDK-2 inhibition. The same is true for MS. Multiple Sclerosis (MS) is a chronic disease of the central nervous system. Viral and autoimmune etiologies have been postulated. While genetic and environmental factors are known to contribute to MS, the skill level in this art is so low that a specific cause for this disease has not been not identified. Corticosteroids, Interferonß-1B (Betaseron) as well as Interferonß-1a

have been used with some limited success. However, so far as the examiner is aware, a) CDK-2 inhibitors have not been successfully employed against MS and b) immunosuppressive agents have not been convincingly established as effective against MS. A great deal of research has gone into the use of immunosuppressive agents for MS, but their use remains very controversial. However, applicants have not established that their compounds actually are immunosuppressive agents. With regard to claim 73, restenosis, or recurrent stenosis, is an extremely general term, referring to a physical process rather than a specific set of diseases. Stenosis is the narrowing of any canal, orifice, valve, duct, artery, vein, tube (such as trachea), opening, etc. in the body. These can arise from obstructive lesions, deposits of granulations, organ hypertrophy, etc. There is no such thing as being able to treat generally such widely diverse problems which arise from different sources. The Sielecki reference doesn't even mention restenosis as a target for CDK2 inhibitors.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here.

The traverse is unpersuasive. Of the four earlier references, Applicants state, "The articles cited by the Examiner are from 1994 and 1995 - much progress has been made in this area since then." First, applicants are asserting an effective filing date of 8/2/1996, which they need to overcome intervening art. Thus, these 1994 and 1995

references are in fact fairly close in time to the relevant date. Applicants cite 6503914, but that reference is not drawn to the CDK2 utility and hence is irrelevant. As for 6498163, that reference only serves to show how ineffective applicants compounds are. The compounds of that reference are not purines at all, and these all actually do inhibit the enzyme. The Table at column 85 shows that about half of the compounds have values below 0.2. Applicants do not have a single compound tested out of their 34 to show a value that low. Indeed, some in the reference are at 0.05 or lower. And, the Sielecki reference is cited to show that in fact, there has been relatively slow progress in the 1994-2000 time period.

Applicants have cited a quotation from *In re Bundy*. First, that was from a context in which the compounds themselves were being held non-enabled, not the case here. Second, the requirement referred to, the "requiring specific testing of the thousands of prostaglandin analogs..." is not being made here. The examiner has in fact not made any testing requirement at all. Third, prostaglandins were already established as effective medicinals as of the filing date. That is not so here. Next applicants cite *In re Gardner* to the effect that "there is no requirement ... that all of the claimed compounds have the same degree of utility." The examiner has made no such requirement. However, it is relevant to point out that many species tested did not inhibit the enzyme at all, and nearly all failed the 0.5 μg/ml standard set forth in the specification. Next, applicants cite *Ex Parte Schundehutte* which says, "It is manifestly impractical for an applicant who discloses a generic invention to give an example of every species falling within it, or even to name every species." The examiner has made no such requirements.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-2, 8, 10, 14-16, 18, 20, 44-48 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 5866702. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims here are just broader versions of those of the grandparent case.

Claims 48-50, 53-62, 65-67 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 92 and others of copending Application No. 09/929772. Although the conflicting claims are not identical, they are not patentably distinct from each other because there is extensive overlap between these two cases which ultimately came from the same application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Specification

The parentage is still not correct. It says "... which is a section 371 application of ..." but in fact, it is a CIP of the PCT application.

This case lacks a proper abstract; the one provided is too brief and gives no clue as to structure of the compounds. Suggested is page 57, but leaving out the last 6 words.

The scheme on page 19 is defective. The three steps must recite a reagent used, not a bare moiety. The same problem occurs on page 36. The traverse is unpersuasive. The scheme is simply not correct. Applicants are again urged to implement the changes which were made in 08/692012 as well, e.g. "bromalino" in the last line of page 31. which is not correct at all, as many of the same errors are here as well.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark L. Berch whose telephone number is 703-308-4718. The examiner can normally be reached on M-F 7:15 - 3:45.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mukund Shah can be reached on 308-4716. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4556 for regular communications and 703-308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 708-308-1235.

Mark L. Berch
Primary Examiner
Art Unit 1624

January 8, 2004